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09/802,232	03/08/2001	Yoshihiko Makino	JG-YY-5052 / 500569.2___	6671

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,232	MAKINO ET AL.	
	Examin r	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communicati n appears on the cov r sh et with th c rrespondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/8/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's RCE filed on March 27, 2003 and the amendment filed December 26, 2002 have been entered. The claims pending in this application are claims 1-20. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on December 26, 2002.

Claim Objections

2. Claim 1 is objected to because of the following informality: please delete the phrase "into contact with an aqueous medium" in line 9 of the claim since, in view of the first step of the claim, this phrase appears to be unnecessary phrase.

3. Claims 10 and 20 are objected to because of the following informality: since claims 1 and 11 require that probe molecule is selected from the group consisting of a nucleic acid or a nucleic acid derivative while claims 10 and 20 require that the probe molecule is selected from the group consisting of oligonucleotide, polynucleotide, and peptide nucleic acid, it appears that claims 10 and 20 does not further limit the subject matter of claims 1 and 11 respectively. The examiner suggests that applicant changes the phrase "the probe molecule is selected from the group

consisting of oligonucleotide, polynucleotide, and peptide nucleic acid" in claims 10 and 20 to "the nucleic acid or the nucleic acid derivative is selected from the group consisting of oligonucleotide, polynucleotide, and peptide nucleic acid" in order to overcome this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 2-10 are dependent on claim 1.

6. Claim 1 is rejected as vague and indefinite in view of step 1 (bringing step) and the phrase "applying variation of a physical or chemical surrounding conditions to the latter aqueous medium" in step 2 (applying step) because the phrase "the latter aqueous medium" lacks sufficient antecedent basis since the first step of the claim only has one aqueous medium and does not have two aqueous media. The examiner suggests that applicant changes "the latter aqueous medium" to "the aqueous medium" in order to overcome this rejection.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 11, 12, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piunno *et al.,* (Anal. Chem., 67, 2635-2643, August 1995) in view of Makino *et al.,* (US Patent No. 6,506,567 B2, filed January 31, 2001).

This rejection is based on that the examiner considers that priority date of this instant application is not March 8, 2000 but is its filing date, March 8, 2001 since applicant does not provide a English translation of its priority document, Japanese patent No. 2000-063129 (filed on March 8, 2000). In the situation that applicant argues that this instant application is English translation of Japanese patent No. 2000-063129, applicant is required to provide a declaration to show that this instant application and Japanese patent No. 2000-063129 is equivalent in order to overcome this rejection. Note that applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The invention is directed to a method for testing complementation of nucleic acid fragment. Claim 11 requires following steps: (1) bringing a sample nucleic acid fragment into contact with a probe molecule fixed to a solid carrier in the presence of an aqueous medium and a labeled intercalator to produce on the solid carrier a sample nucleic acid complex comprising a double-stranded nucleic acid structure and the labeled intercalator intercalated therein, the sample nucleic acid fragment being partly complementary to the probe molecule, the probe molecule being selected from the group consisting of a nucleic acid or a nucleic acid derivative, while applying variation of physical or chemical surrounding conditions to the aqueous medium, so that stability of the sample nucleic acid fragment in the complex is determined, and (2) comparing the stability determined above with reference stability data which are separately obtained by determination of stability of a reference nucleic acid fragment in a reference nucleic acid complex comprising a reference double-stranded nucleic acid structure and the labeled intercalator intercalated therein in which the reference double-stranded nucleic acid structure is produced by contact of the reference nucleic acid fragment with the probe molecule, the reference nucleic acid fragment being determined in complementation thereof with the probe molecule. Since the specification does not define "a labeled intercalator" in claim 11, a labeled intercalator is interpreted as an intercalator labeled with a molecule that is not part of the intercalator. The interpretation is supported by page 19 of the specification wherein an intercalator is labeled with a fluorescence dye and is also supported by pages 12-18 and claim 15 wherein an intercalator (ie., a naphthalene diimide derivative in page 13 of the specification)) having an electroconductive label (ie., metallocene moiety or ferrocene moiety, see page 18, lines 16-36 of the specification). Claim

16 further limits claim 11 and requires that the labeled intercalator is an intercalator having a fluorescent label. Claim 17 further limits the probe molecule and requires that the probe molecule contains a chain of a base sequence comprising least three predetermined base units in series. Claim 18 further limits the reference nucleic acid fragment and requires that the reference nucleic acid fragment contains a chain of a base sequence comprising at least three base units in series which are fully complementary to the chain of the probe molecule. Claim 19 further limits claim 11 and requires that the reference stability data are obtained by a step which is identical to the first step of claim 11, except for replacing the sample nucleic acid complex with the reference nucleic acid complex. Claim 20 requires that the probe molecule is selected from the group consisting of oligonucleotide, polynucleotide, and peptide nucleic acid.

Piunno *et al.,* teach a fiber-optical DNA sensor for fluorometric nucleic acid determination. They teach to detect the association and dissociation of immobilized dT20 with dA20, rA20 and noncomplement DNA (dR19). The hybridization (forming double stranded complexes) was performed in the presence of dT20 immobilized on a optical fiber, dA20, and ethidium bromide and the hybridization was monitored by the use of the fluorescent DNA stain ethidium bromide (see abstract in page 2635, Figures 2, 5 and 6, and Table 1 in page 2642). The dissociation of double stranded complexes were determined by measuring their melting curve and monitored using UV-visible spectrometer (see left columns in page 2639 and 2641, and Figure 3). They also compared melt curves between support-bound dT20-dA20 complex and dT20-dA20 complex in an aqueous phase (see left column in page 2641 and Figure 3).

Regarding claims 11, 12, 19, and 20, since Piunno *et al.,* teach that dT20 immobilized on a optical fiber first hybridizes with dA20 in the presence of ethidium bromide and a hybridization buffer in order to form a dT20-dA20-ethidium bromide complex (see Figure 2), the double stranded nucleic acid complex formed by the hybridization (ie., dT20- dA20) is on a solid carrier (ie., a optical fiber) wherein dT20, dA20, and the hybridization buffer are a probe molecule fixed to a solid carrier, a sample nucleic acid fragment, and an aqueous medium respectively as recited in claim 11. Since dT20- dA20 complex is labeled with ethidium bromide and it is known that ethidium bromide is an intercalator of nucleic acids, the double stranded nucleic acid (ie., dT20-dA20) on a solid carrier (ie., a optical fiber) comprises a double-stranded nucleic acid structure and an intercalator intercalated in the double stranded nucleic acid complexes as recited in claim 11. Although dT20 is fully complementary to dA20, since claim 11 does not limit that the sample nucleic acid fragment (ie., dA20) is **only** partly complementary to the probe molecule (ie., dT20) and the phrase "fully complementary" comprises the scope of "partly complementary", "partly complementary" as recited in claim 11 is taught by Piunno *et al.*. Since Piunno *et al.,* teach that the dissociation of dT20-dA20-ethidium bromide were determined by measuring their melting curve (thermal denaturation) in a hybridization buffer (see left column in page 2639) and it is known that melting curve of a double stranded nucleic acid is commonly used to measure the stability of the double stranded nucleic acid, Piunno *et al.,* teach to determine the stability of the sample nucleic acid fragment (ie., dA20) in a sample nucleic acid complex (ie., dT20-dA20). Since Piunno *et al.,* compare melting curves between support-bound dT20-dA20 complex and dT20-dA20 complex in an aqueous phase (see Figures 2 and 3), Piunno *et al.,* teach to compare

the stability of the sample nucleic acid fragment (ie., dA20) in a sample nucleic acid complex with reference stability data which are separately obtained by determination of stability of a reference nucleic acid fragment in a reference nucleic acid complex wherein dT20 and dA20 in the reference nucleic acid fragment in the aqueous phase are a reference probe molecule and a reference nucleic acid fragment respectively as recited in claim 11 and the reference stability data are obtained by a step which is identical to the first step of claim 11, except for replacing the sample nucleic acid complex (ie.,support-bound dT20-dA20 complex) with the reference nucleic acid complex (ie.,dT20-dA20 complex in the aqueous phase) as recited in claim 19. Since the melting curve is performed using thermal denaturation in temperature ranges of 20 ^{0}C to 80 ^{0}C, the thermal denaturation in varied temperatures is variation of physical or chemical surrounding conditions as recited in claims 11 and 12. Since the hybridization between the probe molecule fixed to a solid carrier and the sample nucleic acid fragment and the hybridization between the reference probe molecule and the reference nucleic acid fragment are performed using the method of Figure 2 (see page 2638), both the sample nucleic acid complex (ie.,support-bound dT20-dA20 complex) and the reference nucleic acid complex (ie.,dT20-dA20 complex in the aqueous phase) are labeled with ethidium bromide. Since the probe molecule is dT20 immobilized on the optical fiber, the dT 20 immobilized on the optical fiber is an oligonucleotide as recited in claim 20.

Regarding claims 17 and 18, since, as described above, dT20 immobilized on the optical fiber is the probe molecule as recited in claim 11 with a known sequences (predetermined), dT20 immobilized on the optical fiber is the probe molecule that contains a chain of a base sequence comprising at least three predetermined base units in series as recited in claim 17. Since, as

described above, dA20 in the aqueous phase is the reference nucleic acid fragment as recited in claim 11 with a known sequences and dA20 is fully complementary to dT20, the dA20 in the aqueous phase is the reference nucleic acid wherein its fragment contains a chain of a base sequence comprising at least three base units in series which are fully complementary to the chain of the probe molecule (ie., dT20) as recited in claim 18.

Since a labeled intercalator is interpreted as an intercalator labeled with a molecule that is not part of the intercalator, ethidium bromide is not a labeled intercalator. Therefore, Piunno *et al.,* do not disclose a labeled intercalator as recited in claims 11 and 16.

Makino *et al.,* teach water-soluble fluorescent intercalator compound as recited in claims 11 and 16. This compound had a formula, F-La-X wherein F was a fluorescent moiety, X was a cyclic group, and La was a linking group (see column 2). The a cyclic group such as naphthalene diimide was used as an intercalator (see column 7). The fluorescent intercalator compound was used to detect a hybrid DNA fragment and measure rate of dissociation of the intercalator from the hybrid DNA fragment (see columns 11 and 12).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used an intercalator having a fluorescence label in the method recited in claims 11. One having ordinary skill in the art would have motivated to do so because Makino *et al.,* have successfully detected a hybrid DNA fragment and measured dissociation rate of the hybrid DNA fragment using an intercalator having a fluorescence label (see Makino *et al.,* columns 11 and 12) and the simple replacement of one known fluorescent intercalator (ie., ethidium bromide) from another known fluorescent intercalator (i.e., an

intercalator having a fluorescence label) in the method for testing complementation of nucleic acid fragment would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

9. Claims 11, 12, 15, and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piunno *et al.,* (1995) in view of Takenaka *et al.,* (Chem. Commun.,10, 1111 and 1112, May, 1998).

The invention is directed to a method for testing complementation of nucleic acid fragment. Claim 11 requires following steps: (1) bringing a sample nucleic acid fragment into contact with a probe molecule fixed to a solid carrier in the presence of an aqueous medium and a labeled intercalator to produce on the solid carrier a sample nucleic acid complex comprising a double-stranded nucleic acid structure and the labeled intercalator intercalated therein, the sample nucleic acid fragment being partly complementary to the probe molecule, the probe molecule

being selected from the group consisting of a nucleic acid or a nucleic acid derivative, while applying variation of physical or chemical surrounding conditions to the aqueous medium, so that stability of the sample nucleic acid fragment in the complex is determined, and (2) comparing the stability determined above with reference stability data which are separately obtained by determination of stability of a reference nucleic acid fragment in a reference nucleic acid complex comprising a reference double-stranded nucleic acid structure and the labeled intercalator intercalated therein in which the reference double-stranded nucleic acid structure is produced by contact of the reference nucleic acid fragment with the probe molecule, the reference nucleic acid fragment being determined in complementation thereof with the probe molecule. Since the specification does not define "a labeled intercalator" in claim 11, a labeled intercalator is interpreted as an intercalator labeled with a molecule that is not part of the intercalator. The interpretation is supported by page 19 of the specification wherein an intercalator is labeled with a fluorescence dye and is also supported by pages 12-18 and claim 15 wherein an intercalator (ie., a naphthalene diimide derivative in page 13 of the specification)) having an electroconductive label (ie., metallocene moiety or ferrocene moiety, see page 18, lines 16-36 of the specification). Claim 15 further limits claim 11 and requires that the labeled intercalator is an intercalator having an electroconductive label. Claim 17 further limits the probe molecule and requires that the probe molecule contains a chain of a base sequence comprising least three predetermined base units in series. Claim 18 further limits the reference nucleic acid fragment and requires that the reference nucleic acid fragment contains a chain of a base sequence comprising at least three base units in series which are fully complementary to the chain of the probe molecule. Claim 19 further limits

claim 11 and requires that the reference stability data are obtained by a step which is identical to the first step of claim 11, except for replacing the sample nucleic acid complex with the reference nucleic acid complex. Claim 20 requires that the probe molecule is selected from the group consisting of oligonucleotide, polynucleotide, and peptide nucleic acid.

The teachings of Piunno *et al.,* have been summarized previously, *supra.*

Since a labeled intercalator is interpreted as an intercalator labeled with a molecule that is not part of the intercalator, ethidium bromide is not a labeled intercalator (see above). Therefore, Piunno *et al.,* do not disclose to use an intercalator having an electroconductive label as recited in claims 11 and 15.

Takenaka *et al.,* teach electrochemically active threading intercalator with high double stranded DNA selectivity (see abstract and Figure 1). They showed that a naphthalene diimide threading intercalator carrying ferrocenyl moieties as its termini such as compound 1 formed a much stable complex with a double stranded DNA than a single stranded DNA and had an ability to conduct electrons (see abstract and right column in page 1111, and Figure 1). Since it is known that naphthalene diimide is an intercalator (see page 1111, left column) and ferrocenyl moieties has an electroconductivity (see the specification, page 18, lines 16-36), and electrochemically active threading intercalator taught by Takenaka *et al.*, has an ability to conduct electrons, the electrochemically active threading intercalator taught by Takenaka *et al.*, (ie., a naphthalene diimide threading intercalator carrying ferrocenyl moieties) is a labeled intercalator having an electroconductive label as recited in claims 11 and 15.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used a labeled intercalator having an electroconductive label in the method recited in claim 11. One having ordinary skill in the art would have motivated to do so because the naphthalene diimide threading intercalator carrying ferrocenyl moieties has been successfully used to label a double stranded DNA and dissociates much more slowly from the double stranded DNA than do classical intercalators (see page 1111, left column, first paragraph), and the simple replacement of one known intercalator (ie., ethidium bromide) from another known intercalator (i.e., naphthalene diimide threading intercalator carrying ferrocenyl moieties such as compound 1) in the method for testing complementation of nucleic acid fragment would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the replacement would enhance stability of a complex formed by double stranded nucleic acid and an intercalator.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

10. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Piunno *et al.,* (1995) in view of Takenaka *et al.,* (1998) as applied to claims 11, 12, 15, and 17-20 above.

The teachings of Piunno *et al.,* and Takenaka *et al.,* have been summarized previously, *supra.* Although Piunno *et al.,* did not directly disclose to dissociate double stranded nucleic acids in the presence of varied ionic strengths, Piunno *et al.*, did suggest that the duplex stability in low ionic strength buffers was less than that in high ionic strength buffers (see left column in page 2641).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 11 in the presence of varied ionic strengths in view of prior art of Piunno *et al.,* and Takenaka *et al.*. One having ordinary skill in the art would have motivated to do so because it was known in the art at the time the invention was made that the duplex stability in low ionic strength buffers is less than that in high ionic strength buffers (see Piunno *et al.,* left column in page 2641) and the simple replacement of a known method (ie., using thermal denaturation taught by Piunno *et al.,*) from another known method (ie., using low ionic strength suggested by Piunno *et al.,*) for measuring stability of a complex formed by double stranded nucleic acid and an intercalator in the method recited in claim 11 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claim 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piunno *et al.,* (1995) in view of Takenaka *et al.,* (1998) as applied to claims 1, 2, 15, and 17-20 above, and further in view of Miller-Jones *et al.,* (WO 98/44100, published on October 8, 1998).

The teachings of Piunno *et al.,* and Takenaka *et al.,* have been summarized previously, *supra.*

Piunno *et al.,* and Takenaka *et al.,* did not disclose to dissociate double stranded nucleic acids using varied electrophoretic potential as recited in claim 13.

Miller-Jones *et al.,* teach disassociation of a double stranded DNA by applying an electrical voltage applied between electrodes (see abstract and claim 1 in page 23). A potential difference was applied across the electrodes for a fixed time period, with or without a number of polarity changes. A typical "profile" was illustrated in FIG. 2 where x=1.2 V t_1 =3 sec and t_2 =1 sec (see page 21, first paragraph and Figure 2). Since the specification does not have a definition for "electrophoretic potential", according to the specification (see page 29, lines 11), "[T]he variation of electrophoretic force can be applied to the complex, for instance, by applying varying electric gradient (potential) between the substrate (electrode) of DNA chip and a counter

electrode (i.e., opposite electrode) which is also placed in contact with the aqueous medium. If the detection is performed using a fluorescent intercalator and using no electrode, a pair of electrodes are placed in the vicinity of the nucleic acid complex or the probe molecule to produce the electrophoretic force", electrophoretic potential as recited in claim 13 is interpreted as a potential difference applied across two electrodes. Since the potential difference applied across the electrodes taught by Miller-Jones *et al.,* is with a number of polarity changes, Miller-Jones *et al.,* teach variation of electrophoretic potential as recited in claim 13.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 11 using varied electrophoretic potential in view of prior art of Piunno *et al.,* Takenaka *et al.,* and Miller-Jones *et al.*. One having ordinary skill in the art would have motivated to do so because Miller-Jones *et al.,* have successfully separated double stranded nucleic acids by applying an electrical voltage applied between electrodes and the simple replacement of a known method (ie., using thermal denaturation from Piunno *et al.,*) from another known method (ie., using electrophoretic potential from Miller-Jones *et al.,*) for measuring stability of a complex formed by double stranded nucleic acid and an intercalator in the method recited in claim 11 would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 4 of applicant's remarks, applicant argued that " [P]iunno et al reference differs significantly from the presently claimed invention and does not provide a proper basis for rejection either under 35 USC 102 or 35 USC 103." since "[P]iunno et al contains no information with respect to the differentiation between the fully complementary relationship to form a full match structure and the partly complementary relationship to form the mismatched structure.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Although Piunno *et al.*, teach that dT20 is fully complementary to dA20, since claim 11 does not limit that the sample nucleic acid fragment (ie., dA20) is **only** partly complementary to the probe molecule (ie., dT20) and the phrase "fully complementary" comprises the scope of "partly complementary", the examiner considers that "partly complementary" as recited in claim 11 is disclosed by Piunno *et al.*.

Conclusion

12. Claims 1-10 appear to be allowable if applicant can overcome above objections and the rejection under 35 USC 112, second paragraph since Piunno *et al.*, do not teach to measure decrease of quantity of the labeled intercalator on the solid support as recited in claim 1.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
June 27, 2003